

---

# Benefits of Antioxidants: May Help Protect Against Heart Disease

Prepared by Annette Dickinson, Ph.D.  
Council for Responsible Nutrition  
June 2002

---

Antioxidants help protect every cell and membrane in the body against the ravages of everyday living, and thus help prevent diseases that result from accumulated damage due to oxidation.

Oxidation is not always a bad thing. Many cycles in the body depend on an interlocking chain of reactions involving both oxidation—in which an electron is lost—and reduction—in which an electron is gained. Electrons are passed back and forth continually in countless metabolic reactions without necessarily generating “oxidative damage.” However, the oxidation of some compounds (such as lipids) can be damaging and some oxidative reactions can produce “free radicals,” which are dangerous because they set up a chain reaction that can rapidly damage a large number of molecules. One way to prevent oxidative damage is to surround the sensitive compound with “antioxidants” that can be offered up as targets of oxidation *instead of* the sensitive compound. They can stop a free-radical chain reaction by the simple act of providing a missing electron. Antioxidants are molecules that can easily and harmlessly give up or accept electrons. That is, antioxidants are *substances that are themselves easily oxidized and that are benign* in their oxidized form. Once oxidized, they are also readily reduced back to their active form, making them available for another round of protection.

In the antioxidant cycle, one antioxidant often hands off electrons to another. Antioxidants thus operate as a team, passing electrons back and forth as necessary in order to prevent unwanted oxidation of sensitive compounds. The antioxidant team includes vitamin E and vitamin C. Some minerals such as selenium are integral components of antioxidant enzymes and thus are recognized to serve an antioxidant function. Other food components have also been shown to be protective. These include carotenoids such as beta-carotene, lutein, and lycopene.

Leading scientists such as Dr. Bruce Ames of the University of California at Berkeley are convinced that increasing the intake of a variety of nutrients, including antioxidant vitamins, could result in “a major improvement in health and an increase in longevity.” Providing these nutrients may be one mechanism by which fruits and vegetables appear to reduce the risk of “degenerative diseases including cancer, cardiovascular disease, cataracts, and brain dysfunction.” (Ames 1998)

From *The Benefits of Nutritional Supplements*, Copyright © 2002  
Council for Responsible Nutrition (CRN). All rights reserved.  
Republication or redistribution of CRN content is expressly prohibited  
without the prior written consent of CRN.

## **Vitamin E May Protect Against Heart Disease**

A large body of experimental study and some clinical research studies indicate a link between intake of the antioxidant vitamin E and a reduced risk of heart disease. The most striking clinical study is the Cambridge Heart Anti-Oxidant Study (CHAOS), a randomized controlled trial that found that vitamin E supplementation was dramatically effective in reducing the risk of heart attacks in patients known to be at high risk. In this study, 1000 men with heart problems were given 400 or 800 IU of vitamin E, and another 1000 men were given a placebo. After 18 months, the number of heart attacks in the vitamin E group was only one quarter of the number in the placebo group. In other words, vitamin E reduced the risk of heart attack by 75 percent. One of the physicians who conducted the trial indicated that he would be “recommending that patients with angina and those who are at risk of heart disease should be given supplementary vitamin E at a high dose.” (Stephens 1996)

The Food and Nutrition Board of the Institute of Medicine published a report on antioxidants in 2000, recommending small increases in vitamin E intake but not recommending higher levels of vitamin E intake for purposes related to heart health, although additional research was encouraged. The report noted that these recommendations could change, depending on the outcome of future research: “Some physicians caring for patients with coronary artery disease are already prescribing vitamin E at doses used in the CHAOS study, 400 or 800 IU...Precisely how vitamin E works at these high doses is not known but could include both antioxidant and nonantioxidant mechanisms. This is an active research area at both the molecular and the clinical levels, and further research is needed.” If the results of ongoing trials are positive, “it may become necessary to review the recommendations for vitamin E intakes in some subgroups of the adult population, especially those in the groups over 50 years of age because increasing age is an important risk factor for heart disease.” (Food and Nutrition Board, 2000)

In an epidemiologic study of more than 11,000 elderly people, researchers at the National Institute on Aging found that users of both vitamin E and vitamin C supplements had a 53 percent decreased risk of mortality from heart disease and a 42 percent decreased risk of all-cause mortality, compared to nonusers. The study subjects were selected from populations in Massachusetts, Iowa, Connecticut, and North Carolina. (Losonczy 1996)

### **Key Scientific Studies**

Researchers in California studied the effect of dietary and supplemental antioxidant intake on the progression of atherosclerosis in 156 men who had previously undergone bypass surgery. Angiograms were done at baseline and after two years, to determine whether atherosclerosis had progressed. Men who were taking 100 IU of vitamin E or more had significantly less progression of atherosclerosis during the study period. (Hodis 1995)

In a study of more than 34,000 postmenopausal women in Iowa, researchers at the University of Minnesota found that high dietary intakes of vitamin E were associated with a 68 percent lower risk of death from heart disease. Vitamin E intake in the top 40 percent of the group was greater than 7.6 IU per day. (Note that this is not a very generous intake, as it represents less than half the current RDA for adults.) There was no effect associated with the use of vitamin E supplements, but relatively few women in this cohort consumed high-dose vitamin E, and there was no information on duration of intake. (Kushi 1996)

In a study of over 2300 men in Quebec, the men who took vitamin supplements had a 70 percent reduced risk of dying from ischemic heart disease and almost a 50 percent lower risk of myocardial infarction. The vitamin that appeared to be most protective was vitamin E. (Meyer 1996)

In the Nurses' Health Study, involving more than 87,000 women, Dr. Meir Stampfer and colleagues at Harvard Medical School and the Harvard School of Public Health reported a 41 percent reduction in risk of heart disease among nurses who had taken vitamin E for more than two years. The researchers noted that a beneficial effect of vitamin E on heart disease "is plausible because of the substantial evidence indicating the importance of oxidation of LDL in atherosclerosis." The average vitamin E intake in the lowest-risk group was 200 IU. (Stampfer 1993)

In the Health Professionals Follow-up Study involving almost 40,000 men, Dr. Eric Rimm and colleagues at the Harvard School of Public Health and Harvard Medical School found that men who had taken vitamin E for more than two years had a 37 percent lower risk of heart disease, compared to men who had not taken supplements of vitamin E. The average level of vitamin E intake in the lowest-risk group was 400 IU. (Rimm 1993)

In a dose-response study, 48 healthy male nonsmokers were given 0, 60, 200, 400, 800, or 1200 IU of vitamin E per day for eight weeks. LDL susceptibility to oxidation decreased in the men receiving 400 IU or more of vitamin E, but not in those receiving lower levels. No side effects were observed from any of these treatments. The minimum amount of vitamin E needed to inhibit LDL oxidation appeared to be 400 IU per day. (Jialal 1995)

In diabetic patients, "the risk of atherosclerosis is three to four-fold higher than in nondiabetic persons and cardiovascular disease is the major cause of premature death." It has been suggested that vitamin E might be useful in decreasing the risk of cardiovascular disease in diabetics. A group of researchers examined the effects of 750 IU of vitamin E supplementation for a period of one year, given as 250 IU three times a day. Serum vitamin E levels almost doubled in the first three months and did not increase further. During vitamin E treatment, there was a decrease in lipoprotein peroxidizability. Within three months after stopping supplementation, serum vitamin E levels returned to baseline. Since the benefits of the supplement are conferred only while supplementation is

continuing, the researchers suggest that “life-long supplementation with vitamin E should be considered in patients with type 1 diabetes.” (Engelen 2000)

Patients with endstage renal disease who require chronic hemodialysis have a high mortality rate, much of which is due to cardiovascular disease. “The cardiovascular-disease mortality rate in this patient group is estimated to be five to 20 times that of the general population.” The increased mortality may be due in part to a high level of oxidative stress. In the SPACE trial, researchers tested the effect of 800 IU per day of vitamin E supplementation on cardiovascular disease in these patients. (SPACE stands for Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease.) In the study, almost 200 patients received the vitamin E supplement or a placebo for a period of about two years. The vitamin E treatment was associated with a significant protective effect against cardiovascular death and non-fatal myocardial infarction (heart attack). (Boaz 2000)

While these studies are encouraging, some studies have shown an effect in men but not women. Other studies involving patients with existing heart conditions have surprised researchers by failing to show a benefit.

In a study of 468 men and women ages 66 to 75 in Britain, men with higher plasma levels of vitamin C, beta-carotene, or vitamin E had less thickening (due to atherosclerosis) of the carotid arteries. No similar effects were observed in the women. This study suggests that “a high antioxidant vitamin status may help to prevent the initiation and progression of early atherosclerotic lesions in men.” (Gale 2001)

In the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study in Finland, researchers studied the effect of supplementation with vitamin E and vitamin C on the progression of carotid atherosclerosis, over a period of three years. Subjects received 136 IU of vitamin E twice a day, 250 mg of slow-release vitamin C twice a day, both, or a placebo. The combination of both nutrients slowed the progression of carotid atherosclerosis in men but not in women. (Salonen 2000)

In the Primary Prevention Project (PPP) in Italy, almost 4500 people with at least one major risk factor for heart disease were given low dose aspirin (100 mg) or vitamin E (300 mg) or both, for three to six years. Aspirin lowered the frequency of cardiovascular events and cardiovascular deaths, but vitamin E did not. (PPP 2001)

In the Heart Outcomes Prevention Evaluation study (the HOPE study), researchers enrolled over 2500 women and almost 7000 men over 55 years of age who had existing heart disease or diabetes plus one additional risk factor for heart disease. They were given 400 IU of natural vitamin E (or a placebo) daily for a period of four to six years. There were no significant effects of vitamin E on the risk of heart attacks, stroke, or death. This dose of the vitamin was “well tolerated, with no significant adverse events as compared with placebo.” The HOPE study is being continued “to evaluate the effects of vitamin E on the incidence of cancer.” (HOPE 2000)

In the GISSI trial in Italy, researchers gave 300 mg of vitamin E and/or one gram of omega-3 fatty acids or no supplement to over 11,000 patients who had survived a recent myocardial infarction (heart attack). (GISSI stands for the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico.) The supplements were continued for an average of 3.5 years. The omega-3 fatty acid treatment reduced the risk of death, nonfatal heart attack, and stroke, but the vitamin E did not have a significant protective effect. The authors conclude that “the dose of vitamin E that is most effective and safe, as well as the minimum duration of treatment that is required to produce the postulated protective effects of vitamin E are still unknown.” (GISSI 1999)

The Alpha-Tocopherol Beta-Carotene Study (ATBC) was designed to test whether vitamin E and/or beta-carotene supplementation would reduce the risk of lung cancer in almost 30,000 smokers in Finland, but effects on coronary artery disease were also evaluated. In that study, neither supplement was found to be protective against lung cancer or heart disease. Vitamin E appeared to have a protective effect against prostate cancer, colorectal cancer, and ischemic stroke, but increased the risk of hemorrhagic stroke. (ATBC 1994) The Food and Nutrition Board of the Institute of Medicine in its report on Dietary Reference Intakes for antioxidant nutrients commented: “The unexpected finding of an increase in hemorrhagic stroke in the ATBC study was considered preliminary and provocative, but not convincing until it can be corroborated or refuted in further large-scale clinical trials.” Several other major trials using higher levels of vitamin E have not reported any increased risk of stroke. (Food and Nutrition Board 2000)

Several ongoing clinical trials are now investigating the relationship between supplements of antioxidant vitamins and the risk of heart disease. In the United States, the Women's Health Study is testing the effect of vitamin E and low-dose aspirin in protecting against heart disease (and cancer) in 40,000 healthy female health professionals. The Women's Antioxidant Cardiovascular Disease study is testing vitamin C, vitamin E, and beta-carotene in 8000 women with existing vascular disease or with several coronary risk factors. The Physicians' Health Study is being continued, to determine the effect of beta-carotene on heart disease risk, and multivitamins and vitamin E are being added to the study design.

## **Evaluation of Current Findings**

Drs. Ishwarlal Jialal and Sridevi Devaraj of the University of Texas Southwestern Medical Center and Dr. Maret Traber of the Linus Pauling Institute at Oregon State University, three recognized experts in antioxidants and heart disease, recently posed the question whether there is a “vitamin E paradox.” After critical appraisal of the five major prospective clinical trials on vitamin E (alpha tocopherol) and cardiovascular disease, the authors pointed out that, while the CHAOS and SPACE studies showed a reduction in cardiovascular death and/or nonfatal MI, “the GISSI and ATBC studies also demonstrated benefit on certain end-points, despite the primary end-point not being significant.” Only the HOPE study failed to find a positive effect on any end-point. They concluded that “the totality of evidence based on the epidemiologic data, in-vitro

studies and animal models, and the clinical trials appears to support a benefit for alpha tocopherol supplementation in patients with pre-existing cardiovascular disease.” (Jialal 2001)

The American Heart Association (AHA) notes that most observational studies of antioxidants and disease prevention have focused on antioxidant-rich foods, but “some recent observational studies have suggested the importance of levels of vitamin E intake achievable only by supplementation.” Also, some studies in people who already have evidence of heart disease (secondary prevention trials) have shown beneficial effects of vitamin E. AHA recommends that the general population “consume a balanced diet with emphasis on antioxidant-rich fruits and vegetables and whole grains.” AHA recognizes that such diets “may not provide the levels of vitamin E intake that have been associated with the lowest risk in a few observational studies,” but argues that a specific recommendation for vitamin E supplementation must await additional clinical trials. (American Heart Association 1999)

Drs. Eric Rimm and Meir Stampfer of Harvard Medical School and the Harvard School of Public Health concluded in a broad review of the evidence that “results from observational and experimental studies consistently support an effect of vitamin E supplementation on reducing risk of coronary heart disease. The evidence suggests that the major effect, if any, is found at supplemental intake levels at or greater than 100 IU/d.” They indicate that “the net benefit of vitamin E supplementation among populations with existing coronary disease may be substantial,” although more evidence is needed. (Rimm and Stampfer 2000)

Dr. William Pryor of Louisiana State University concluded in a review article that there is sufficient evidence on vitamin E and heart disease “to recommend modest vitamin E supplementation (100 to 400 IU per day) as part of a general program of heart-healthy behavior that includes a fruit- and vegetable-rich diet and regular exercise.” (Pryor 2000)

### **Goals for Future Research: Dr. Steinberg**

Dr. Daniel Steinberg of the University of California at San Diego, a leading researcher in the area of antioxidants and heart disease, recently posed the question, “Is there a potential therapeutic role for vitamin E or other antioxidants in atherosclerosis?” His answer was, “Probably, but it is too soon to say.” Below are some of the points he emphasized. (Steinberg 2000)

“A large body of evidence supports the hypothesis that oxidation of low-density lipoprotein (LDL) plays an important causative role in the atherosclerosis of several different animal models.” Also, many studies demonstrate that supplementation of humans with vitamin E has effects on “markers” for cardiovascular disease. However, clinical trials of vitamin E in patients with pre-existing heart disease have been disappointing. Dr. Steinberg says it is “most unlikely that further studies in similar patient populations will change the conclusion that was reached, namely, that these doses of vitamin E in patients like these (i.e., with established severe coronary disease) will be

ineffective, at least within a 3-5 year period.” Dr. Steinberg suggests “we may not be doing the right kind of clinical trial” and offers three possible explanations for the negative results of several clinical trials.

1. Vitamin E may inhibit the early stages of atherosclerosis but have little or no effect on advanced lesions. The animal data show a benefit of antioxidants given at very early stages of atherosclerosis, not at late stages. Dr. Steinberg suggests intervention trials that focus on detecting and quantifying the development of new lesions. “The epidemiologic data showing decreased CHD risk in patients with higher intakes or higher plasma levels of vitamin E reflect lifetime exposure to diets associated with higher intakes of vitamin E (or long-term use of supplements). There is no reason to expect that a 3-5-year treatment with supplemental vitamin E can duplicate the protective effect of a lifetime of exposure to, for example, a Mediterranean diet.”
2. Vitamin E may not be the most potent antioxidant for this purpose. Other antioxidant compounds, including synthetics, need further study. “More basic research is needed on the issues of where antioxidant activities are needed *in vivo* and how antioxidants can best be transported to those sites. At the moment, most investigators assume that oxidation in the wall of the artery itself is the most relevant but this has never been firmly established.”
3. There could be a true species difference such that antioxidants shown to be effective in animal models “will simply never have an effect on atherogenesis in humans.” This is a possibility that should not be accepted until the first two explanations are thoroughly explored, but it cannot be ruled out.

Dr. Steinberg concluded that the disappointing results of recent clinical trials “lead us to re-examine the question of what might be the appropriate nature of trials in humans, but they do not invalidate the large body of experimental evidence supporting the role for oxidative modification of LDL in atherogenesis.” (Steinberg 2000)

### **Additional Consideration for Future Research: Selecting Subjects With Evidence of Oxidative Stress**

In order to identify possible effects of vitamin E on lipid peroxidation in healthy people, one group of researchers divided 30 adults into six groups. Each subgroup of five people was assigned to receive a placebo or a daily supplement of 200, 400, 800, 1200, or 2000 IU of vitamin E for eight weeks. Although serum levels of vitamin E increased as expected, there were no changes in three measures of lipid peroxidation. The authors suggested that screening subjects for evidence of oxidative stress may be an important aspect of designing future clinical trials involving antioxidants. (Meagher 2001)

Another researcher also stressed the view that clinical trials on antioxidants “should involve subjects with evidence of increased oxidative stress, just as the statin trials studied subjects with high cholesterol levels rather than the general population....Such a rational approach to therapy has worked well in other fields and is likely to accelerate

progress in the treatment of oxidative stress and coronary heart disease.” (Heinecke 2001)

Dr. Barry Halliwell of the National University of Singapore made similar observations, saying: “The hypothesis behind intervention trials with vitamin E is that lipid peroxidation is a major contributor to atherosclerosis and cardiovascular disease (which I believe), and that administration of vitamin E will decrease the extent of lipid peroxidation and be protective against cardiovascular disease.” He pointed out that none of the clinical trials have sought to demonstrate whether patients in fact had high rates of lipid peroxidation and whether vitamin E lowered lipid peroxidation. Just as physicians do not give antihypertensive drugs to patients without checking their blood pressure, “why should we give antioxidants without checking that they have decreased oxidant status?” (Halliwell 2000)

### **Bottom Line**

---

A number of epidemiological studies show that people with high intakes of vitamin E have a lower risk of heart disease. A dose-response study indicates that at least 400 IU of vitamin E is needed to prevent the oxidation of LDL, and a clinical trial found a dramatically reduced risk of a new heart attack in men with a history of heart disease. Other clinical trials were disappointing. Additional controlled trials are ongoing, and some experts believe it makes sense to take supplemental vitamin E even while further research continues.

---

### **References:**

American Heart Association. Antioxidant consumption and risk of coronary heart disease: emphasis on vitamin C, vitamin E, and beta-carotene: a statement for health care professionals from the American Heart Association, 1999. On the web at [www.americanheart.org](http://www.americanheart.org).

Ames BN. Micronutrients prevent cancer and delay aging. *Toxicology Letters* 1998; 102-103:5-18.

ATBC (The Alpha-Tocopherol, Beta-carotene Cancer Prevention Study Group). The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *New Engl J Med* 1994; 330:1029-1035.

Boaz M, Smetana S, Weinstein T, Matas Z, Gafter U, Iaina A, Knecht A, Weissgarten Y, Brunner D, Fainaru M, Green MS. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomized placebo-controlled trial. *Lancet* 2000; 356:1213-1218.

Engelen W, Keenoy BM, Vertommen J, De Leeuw I. Effects of long-term supplementation with moderate pharmacologic doses of vitamin E are saturable and reversible in patients with type 1 diabetes. *Am J Clin Nutr* 2000; 72:1142-1149.

Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. National Academy Press, Washington, D.C., 2000.

Gale CR, Ashurst HE, Powers HJ, Martyn CN. Antioxidant vitamin status and carotid atherosclerosis in the elderly. *Am J Clin Nutr* 2001; 74:402-408.

GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999; 354:447-455.

Halliwell B. The antioxidant paradox. *Lancet* 2000; 355:1179-1180.

Heinecke JW. Is the emperor wearing clothes? Clinical trials of vitamin E and the LDL oxidation hypothesis. *Arterioscler Thromb Vasc Biol* 2001; 21:1261-1264.

Hodis HN, Mack WJ, LaBree L, et al. Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis. *J Am Med Assn* 1995; 273:1849-1854.

HOPE (The Heart Outcomes Prevention Evaluation Study Investigators). Vitamin E supplementation and cardiovascular events in high-risk patients. *New Engl J Med* 2000; 342:154-160.

Jialal I, Traber M, Devaraj S. Is there a vitamin E paradox? *Curr Opin Lipidol* 2001; 12:49-53.

Jialal I, Fuller CJ, Huet BA. The effect of alpha-tocopherol supplementation on LDL oxidation: a dose-response study. *Arteriosclerosis, Thrombosis & Vascular Biology* 1995; 15:190-198.

Kushi LH, Folsom AR, Prineas RJ, et al. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *N Engl J Med* 1996; 334:1156-1162.

Losonczy KG, Harris TB, Havlik RJ. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the established populations for epidemiologic studies of the elderly. *Am J Clin Nutr* 1996; 64:190-196.

Meyer F, Bairati I, Dagenais GR. Lower ischemic heart disease incidence and mortality among vitamin supplement users. *Can J Cardiol* 1996; 12:930-934.

PPP (Primary Prevention Project). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *Lancet* 2001; 357:89-95.

Pryor WA. Vitamin E and heart disease: basic science to clinical intervention trials. *Free Rad Biol & Med* 2000; 28:141-164.

Rimm EB, Stampfer MJ. Antioxidants for vascular disease. *Medical Clinics of North America* 2000; 84:239-249.

Rimm EB, Stampfer MJ, Ascherio A, et al. Vitamin E consumption and the risk of coronary heart disease in men. *New Engl J Med* 1993;328:1450-1456.

Salonen JT, Nyssonen K, Salonen R, et al. Antioxidant supplementation in atherosclerosis prevention (ASAP study: a randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis). *J Internal Med* 2000; 248:377-386.

Stampfer MJ, Hennekens CH, Manson JE, et al. Vitamin E consumption and the risk of coronary disease in women. *New Engl J Med* 1993;328:1444-1449.

Steinberg D. Is there a potential therapeutic role for vitamin E or other antioxidants in atherosclerosis? *Curr Opin Lipidol* 2000; 11:603-607.

Stephens NG, Parsons A, Schofield PM, et al. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* 1996; 347:781-786.